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| EXAMINER | |
|---|---|
| SHAW, AMANDA MARIE | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/537,562 | VENEMA, FOKKE | |
| | Examiner | Art Unit | |
| | Amanda Shaw | 1634 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☐ Responsive to communication(s) filed on *12/1/2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *24,25,28,29,32,33,36,37,40,41,43,44,47-50,54,55 and 57-64* is/are pending in the application.

4a) Of the above claim(s) *24,25,28,29,32,33,36 and 37* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *40,41,43,44,47-50,54,55 and 57-64* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

**DETAILED ACTION**

1. This action is in response to the amendment filed December 1, 2009. This action is made FINAL.

Claims 24-25, 28-29, 32-33, 36-37, 40-41, 43-44, 47-50, 54-55, and 57-64 are currently pending.

Claims 40, 41, and 47-50 have been amended.

Claims 57-64 are newly presented.

Claims 24-25, 28-29, 32-33, and 36-37 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected subject matter, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on March 25, 2008.

***Claim Rejections - 35 USC § 102***

2. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 40, 44, 47, and 54 are rejected under 35 U.S.C. 102(a) and (e) as being anticipated by Beckman (US 2003/0134307 Pub 7/2003 and filed 10/2002).

Regarding Claim 40 Beckman teaches molecular beacon (MB) probes comprising modified nucleotides. Specifically Beckman teaches that a MB probe comprising standard deoxyribonucleotides can also comprise one or more 2'-O-methyl nucleotides (e.g., at its 5'end) (para 0074). In the instant case Beckman anticipates a MB probe wherein the one 2'-O-methyl nucleotide can be present at any position including the 3' strand of the stem. Thus Beckman teaches a MB probe comprising a stem with one or more unmodified nucleotide and in the 3' strand of the stem one 2'-O-methyl nucleotide. Additionally Beckman exemplifies a probe wherein each base pair of the stem comprises no more one 2'-O-methyl nucleotide since the MB only has a single 2'-O-methyl nucleotide. Further it is an inherent property of this probe that it has better stability and does not open spontaneously in the presence of contaminants present in an amplification enzyme mixture comprising said molecular beacon probe compared to a molecular beacon probe without said stem.

Regarding Claim 44 Beckman teaches a MB probe wherein the 2'-O-derivatized nucleotide is a 2'-O-methyl nucleotide (para 0074).

Regarding Claim 47 Beckman teaches that a MB probe comprising standard deoxyribonucleotides can also comprise one or more 2'-O-methyl nucleotides (e.g., at its 5'end) (para 0074). In the instant case Beckman anticipates a MB probe wherein the one 2'-O-methyl nucleotide can be present at any position including the 3' strand of the stem. Additionally Beckman exemplifies a probe wherein at least one base pair of said

stem contains no nucleotide or nucleotide analog having an affinity increasing modification since the MB only has a single 2'-O-methyl nucleotide.

Regarding Claims 54 Beckman teaches a kit comprising primers, polymerase, reagents for performing amplification of an analyte, and a molecular beacon (para 0086).

***Claim Rejections - 35 USC § 103***

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 41, 43, 48-50, 55, and 57-64 are rejected under 35 U.S.C. 103(a) as being unpatentable over Beckman (US 2003/0134307 Pub 7/2003 and filed 10/2002) in view of Majlessi (Nucleic Acids Research 1998) and Tsourkas (Nucleic Acids Research 2002).

The teachings of Beckman are presented above. It is reiterated that Beckman teaches that a MB probe can comprise one or more 2'-O-methyl nucleotides or a MB probe can consist entirely of 2'-O-methyl nucleotides (para 0074).

Beckman does not specifically teach of the MB configurations recited in claims 41, 43, 48-50, 55, 57-64.

However Majlessi teaches that 2'-O-methyl oligoribonucleotide probes afford multiple advantages over 2' deoxy oligoribonucleotide probes for detecting RNA targets, including greatly increased Tm which allows use of shorter probes, faster kinetics of hybridization, ability to bind to structured targets under conditions where 2' deoxy oligoribonucleotide probes will not and significantly improved specificity. Majlessi further states that these advantages render 2'-O-methyl oligoribonucleotide probes superior to 2' deoxy oligoribonucleotide probes for use in assays that detect RNA targets (page 2224 and 2229). Thus the benefits of using 2'-O-methyl modified probes were well known in the art at the time of the invention.

Additionally Tsourkas teaches that 2'-O-methyl oligoribonucleotides bind RNA with higher affinity and faster kinetic hybridization rates, resist nuclease degradation, and do not form a substrate fro Rnase H. Tsourkas further teaches that 2'-O-methyl MB probes form a more stable stem-loop structure because of the presence of the 2'-O-methyl nucleotides. In the absence of target, the 2'-O-methyl MB exhibited a higher Tm and a lower level of background fluorescence compared with the 2' deoxy MB. The 2'-O-methyl modification of the MB backbone resulted in a higher affinity for target mRNA. The melting temperature of the 2'-O-methyl/RNA hybrid was found to be significantly higher than that of the 2'-deoxy/RNA hybrid (page 5173). Thus the benefits of using 2'-O-methyl modified probes were well known in the art at the time of the invention.

While Beckman does not exemplify each and every probe configuration recited by the claims designing probes which are equivalents to those being claimed is considered routine experimentation especially since MB probes comprising standard

deoxyribonucleotides and one or more 2'-O-methyl nucleotides had already been described by Beckman. Further the advantages of using probes comprising 2'-O-methyl nucleotides were already known in the prior art and are taught by Majlessi and Tsourkas. Although Majlessi and Tsourkas compared probes consisting of 2'-O-methyl oligoribonucleotides to probes consisting of 2' deoxy oligoribonucleotides one of skill in the art would have recognized that probes consisting of both 2'-O-methyl nucleotides and 2' deoxy oligoribonucleotides would also be useful. Thus the prior art is replete with guidance and information necessary to permit the ordinary artisan to design MB probes that have better stability and do not open spontaneously (because the stem region comprises 2'-O-methyl nucleotides) and probes that are more sensitive to polymorphisms (because the loop region comprises 2'-O-methyl nucleotides). Based on the computer programs available an ordinary artisan would have had more than a reasonable expectation of success of designing the probes that have better stability and do not open spontaneously and probes that are more sensitive to polymorphisms. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

### *Response To Arguments*

4. In the response filed December 1, 2009, Applicants stated that they amended claim 40 to overcome the rejection made under 35 USC 102. The Applicants state that

the claim now requires that the one or more nucleotides or nucleotide analogs having the affinity increasing modification is present in the 3' strand of the stem.

This argument has been fully considered but is not persuasive. Beckman teaches molecular beacon (MB) probes comprising modified nucleotides. Specifically Beckman teaches that a MB probe comprising standard deoxyribonucleotides can also comprise one or more 2'-O-methyl nucleotides (e.g., at its 5'end) (para 0074). In the instant case Beckman anticipates a MB probe wherein the one 2'-O-methyl nucleotide can be present at any position including the 3' strand of the stem. Thus the rejections are maintained.

The Applicants also traversed the rejection made under 35 USC 103 over the combination of Beckman, as evidenced by Majlessi and Tsourkas. First the Applicants reiterated why they believe that Beckman does not teach a MB probe comprising one or more nucleotides or nucleotide analogues having an affinity increasing modification in the 3' strand of the stem.

Applicant's arguments regarding the Beckman reference have been fully addressed above. The response to Applicants arguments as set forth above applied equally to the present grounds of rejection.

The Applicants state that Majlessi does not teach MB probes but rather linear probes consisting entirely of 2'-O-methyl nucleotides. They state that Majlessi found that there are advantages of using probes consisting entirely of 2'-O-methyl nucleotides over those consisting entirely of 2'-O-deoxynucleotides. Thus Applicants submit that Majlessi

fails to provide one of ordinary skill in the art any motivation to produce the MB probes of the present invention.

This argument has been fully considered but is not persuasive. In the instant case Majlessi is being relied upon to demonstrate that it was well known in the art at the time of the invention that there were advantages to using probes comprising 2'-O-methyl oligoribonucleotides over 2' deoxy oligoribonucleotides. The Examiner acknowledges that Majlessi refers to linear probes however the reference is relevant to the instant invention. Majlessi teaches that 2'o-methyl oligoribonucleotide probes bound to RNA targets faster and with much higher melting temperatures than corresponding 2'-deoxyribonucleotide probes (abstract). This teaching is important because it describes the base pairing of a 2'-o-methyl nucleotide and a unmodified nucleotide which is required by the present claims since each base pair in the stem comprises no more than one 2'-o-methyl nucleotides. Further the fact that Majlessi does not teach probes having a combination of 2'-O-methyl nucleotides and 2'-deoxy nucleotides is irrelevant because Beckman clearly teaches MP probes that have a combination of 2'-O-methyl nucleotides and 2'-deoxy nucleotides.

The Applicants state that Tsourkas describes MB probes consisting entirely of 2'-O-methyl nucleotides or consisting entirely of 2' deoxy nucleotides. The Applicants acknowledge that Tsourkas also discusses the advantages of probe comprised entirely of 2'-O-methyl nucleotides as compared with probes comprised entirely of 2'deoxynucleotides and the ability of the 2'-O-methyl nucleotide MB probes to hybridize with higher affinity and faster kinetic hybridization rates to the target nucleic acid as

compared with 2'-deoxynucleotide MB probes. They state that Tsourkas teaches that the stem loop structure of a 2'-O-methyl nucleotide MB probe is more stable than the stem loop structure of a 2'-deoxynucleotide MB. Thus Applicants state that one reading Tsourkas would not be motivated to make the MB probes of the present invention because Tsourkas teaches away from the present invention.

This argument has been fully considered but is not persuasive. Tsourkas is being relied upon to demonstrate that it was well known in the art at the time of the invention that there were advantages to using MB probes comprising 2'-O-methyl nucleotides over unmodified nucleotides. Tsourkas teaches that "We found that the 2-o-methyl molecular beacons hybridize to RNA more quickly and with higher affinity than 2'-deoxy molecular beacons even though they exhibit a much more stable stem-loop structure. However, the enhanced affinity between 2'-o-methyl molecular beacons and RNA is accompanied by a slightly reduced ability to discriminate between wild type and mutant targets". The argument that Tsourkas teaches away from the claimed invention is misleading because Tsourkas merely states that there is a trade off between using a MB probe consisting of only 2'-O-methylnucleotides compared to the MB probe consisting of only 2'-deoxynucleotides. While there may be a slightly reduced ability to discriminate one would gain the added benefit of faster hybridization and a higher affinity. Further Tsourkas is silent with regard to probes having both types of nucleotides. As such one of skill in the art would not necessarily be lead away from the claimed invention based on the teachings of Tsourkas.

Next the Applicants state that as present in the previous office action the modified nucleotide of the MP probe of Beckman would be in the 5' end of the probe. The state that the such a structure would fail to block the nuclease activity of Taq polymerase but that such a structure would block true exonucleases. Thus they submit that one of skill in the art would not be motivated to provide a MB having a modified nucleotide in the 3' strand of the stem because such a probe would be more sensitive to attack from nucleases.

This argument has been fully considered but is not persuasive. As stated above Beckman teaches molecular beacon (MB) probes comprising modified nucleotides. Specifically Beckman teaches that a MB probe comprising standard deoxyribonucleotides can also comprise one or more 2'-O-methyl nucleotides (e.g., at its 5'end) (para 0074). In the instant case Beckman anticipates a MB probe wherein the one 2'-O-methyl nucleotide can be present at any position including the 3' strand of the stem. Further if the MB probe was being used for the sole purpose of hybridization (and hybridization solutions don't typically contain nucleases) then it wouldn't matter if the modified nucleotide was in the 3' strand of the stem.

Finally the Applicants argue that none of the cited references provide any reasonable expectation of success in constructing the claimed MB. The Applicants state that they have surprisingly discovered that the designing of a MB probe having better stability that does not open spontaneously depends not only on the presence of nucleotide analogues in the stem but also on the number of nucleotide analogues, their position in the stem or loop of the MB probe and the sequence of the stem or loop of the

MB probe. The Applicants refer to, Table 6 of Example 4 which shows that the MB4 probe having all modified nucleotides has a greater percentage of spontaneous opening (IBL- Increase of Baseline) than reference MB which is comprised entirely of unmodified nucleotides. The MB4 probe having all modified nucleotides also has a greater percentage of spontaneous opening as compared to MB probes comprising a combination of unmodified and modified nucleotides. Furthermore, as shown by the other MB probes provided in Table 6, the position and number of nucleotide analogues in the probe are clearly shown to affect rates of spontaneous opening. None of the cited art teaches or suggests that the content and placement of the modified nucleotides in an MB probe would play an important role in the functional features of the MB probe.

This argument has been fully considered but is not persuasive. First of all there is more than a reasonable expectation of the success in designing the claimed probes. In the instant case the binding properties of 2'O-methyl nucleotides with each other and with 2'-deoxynucleotides were well known in the art as disclosed by Majlessi and Tsourkas. Further MB probes having one or more 2'O-methyl nucleotides were well known in the art as disclosed by Beckman. Thus the prior art is replete with guidance and information necessary to permit the ordinary artisan to design MB probes that have better stability and do not open spontaneously (because the stem region comprises 2'-O-methyl nucleotides) and probes that are more sensitive to polymorphisms (because the loop region comprises 2'-O-methyl nucleotides). Through routine optimization it would be obvious to designing probes in the configurations that are claimed. Further there are computer programs available that aid in the selection and design of such

probes. For this reason an ordinary artisan would have had more than a reasonable expectation of success of designing the probes that have better stability and do not open spontaneously and probes that are more sensitive to polymorphisms.

***Conclusion***

5. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amanda M. Shaw whose telephone number is (571) 272-8668. The examiner can normally be reached on Mon-Fri 7:30 TO 4:30. If attempts to reach the examiner by telephone are unsuccessful, the examiner's

supervisor, Dave Nguyen can be reached at 571-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Amanda M. Shaw
Examiner
Art Unit 1634

/Stephen Kapushoc/
Primary Examiner, Art Unit 1634